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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/045,400	11/29/2001	Chulso Moon	P-CAN 1004	4431

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EXAMINER	
YU, MISOOK	

ART UNIT	PAPER NUMBER
1642	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/045,400	MOON ET AL.	
	Examiner	Art Unit	
	MISOOK YU	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 April 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,43-48,50-56 and 58-66* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *52,55, 56,58-60 and 64-66* is/are allowed.

6)☒ Claim(s) *1,43,48,53,54 and 61* is/are rejected.

7)☒ Claim(s) *44-47,50-52,61 and 62* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant is advised that the Notice of Allowance mailed on 10/26/2006 is vacated, in view of further consideration. Prosecution on the merits of this application is reopened on claims 1, 43, 48, 53, 54, and 61, which are considered unpatentable for the reasons indicated below: Any inconvenience experienced by applicant is regretted.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 53, 54, and 61 are rejected under 35 U.S.C. 102(b) as being anticiapted by Esteller et al., of record (1999, IDS, pages 67-70)

Claim 53. A method of assessing aggressiveness of a NSCLC tumor in a human comprising assessing expression of the gene encoding DAP-kinase in lung cells of the human, whereby a lower degree of expression of the gene is an indication that the tumor is aggressive.

Claim 54. The method of claim 53 wherein the tumor is a diagnostic stage I NSCLC tumor.

Claim 61. The method of claim 53 wherein expression of the gene is assessed by assessing methylation of the gene's promoter.

Esteller et al (1999) teaches a method of assessing NSCLC tumorigenesis at various stages including in early stage in human comprising assessing expression of the gene encoding DAP-kinase in lung cells of the human patients with NSCLC. See the *Abstract* and *Materials and Methods* on page 67 and *Results* on page 68. The incidence of DAP-kinase promoter hypermethylation was observed in 5 of the 22 patients. See the Patient Numbers 1, 64, 84, 106 and 112, wherein patients 84 and 106

have an early stage, i.e., diagnostic stage I NSCLC tumor. See Table 1. In contrast, **none** of the 22 paired lung **normal** tissues exhibited abnormal promoter hypermethylation of any gene. See page 68, second column, the last sentence of the top paragraph.

Esteller et al also state that silencing of tumor suppressor genes by promoter hypermethylation is a common feature in human cancer. Moreover, the loss of expression of the DAP kinase gene had been correlated with metastatic potential in experimental lung cancer models. On the basis of these observations, they examined 22 NSCLC patients to detect abnormal promoter hypermethylation in genes including DAP kinase in primary tumors. See the third paragraph at the second column on page 67.

Though, Esteller et al did not explicitly state that they were trying to assess the aggressiveness of a NSCLC tumor in a human comprising assessing the gene encoding DAP-kinase in lung cells of the human, the method taught by Esteller et al comprises assessing expression of the gene encoding DAP-kinase in lung cells of human via the assessment of methylation of the gene's promoter, and a lower degree of expression of the gene (e.g., methylation of the gene) in patients afflicted with NSCLC was observed. Thus, Esteller et al teaches every limitation of the instantly claimed method, and the prior art's observation of the lower degree of expression of the gene {indicated by the abnormal hypermethylation of the promoter region of the tumor DNA for DAP-kinase when compared to those in paired normal lung tissue that does not hypermethylate the equivalent DNA} must be indicative that the tumor is aggressive.

On page 67 (see 2nd full paragraph of 2nd Column) of Esteller et al. the DAP kinase gene has been correlated with metastatic potential. Of the 5 patients that demonstrated differential expression of DAP, one patient died of the disease. Finally applicants in their own application (see paragraph 0047 of US 2003/0224509-the published application of the instant application) set forth that the "Thus association of DAP kinase expression with metastatic tendency is known, and it can be concluded that DAP-kinase functions, directly or indirectly, as a metastatic suppressor". Metastatic tendency is an indicator of aggressiveness as acknowledged in the specification (see

paragraph 0034). Therefore, applicant admits the concept of the association of DAP kinase expression with metastatic tendency is known, and Esteller et al. additionally teaches that the association of DAP kinase gene with metastatic potential in lung cancer is known, and teaches the death of 1/5 patients who had differential expression of the DAP kinase gene.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 43, 48, 53, 54, and 61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Esteller et al of record (IDS, 1999).

Claim 1. A method of diagnosing non-small cell lung cancer (NSCLC) in a human, the method comprising assessing expression of the gene encoding DAP-kinase in lung cells of the human, whereby a lower degree of expression of the gene in the human relative to a normal level of expression of the gene in humans not afflicted with NSCLC is an indication that the human is afflicted with NSCLC.

Claim 43. The method of claim 1 wherein expression of the gene is assessed in vitro in cells obtained from the human.

Claim 48. The method of claim 1 wherein expression of the gene is assessed by assessing methylation of the gene's promoter.

See the teachings of Esteller et al above. Further, the reference teaches that the incidence of DAP-kinase in the 5 out of the22 cases is suggestive that this is a common epigenetic alteration in lung cancer, whereas none of the 22 paired lung normal tissues exhibited abnormal promoter hypermethylation of any gene. However, Esteller et al does not explicitly provide normal level of expression of the gene in humans **not** afflicted with NSCLC.

Nevertheless, Esteller et al teaches that the lower degree of expression through hypermethylation of the gene encoding DAP-kinase in lung cells of the human is an indication for lung cancer and that hypermethylation of normally unmethylated CpG islands in many tumor suppressor genes correlates with loss of expression (page 69, second paragraph of the *Discussion*).

Thus, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to apply the method of diagnosing NSCLC in a human of Esteller et al by comparing the results obtained from the sample cases with a human that is known not to be afflicted with NSCLC, since the reference teaches that they have used paired lung normal tissue, with the reasonable expectation that the control normal lung tissues would not show hypermethylation, as the knowledge seem to have been well established in the art.

Estellar et al. teaches that DAP kinase is one of several markers whose level of expression appear to be useful diagnostic markers for NSCLC. Estellar et al. teaches the incidence of DAP kinase promoter hypermethylation was 23% suggesting that this is a common epigenetic alteration in lung cancer (see page 68; Column 2; lines 1-5). Beyond this it would be expected that one of ordinary skill in the art would have used this marker in combination with other markers to be useful for detecting more patients. Esteller et al. teaches the analysis of abnormal promoter methylation status of several genes in a timely and economic fashion, combined with the study of previously described genetic alterations, may allow the detection of almost all patients with circulation tumor DNA (see page 69 and 70). Finally Esteller et al. there approach allows sensitive and accurate detection of circulating tumor DNA and may have multiple applications in the follow-up and management of cancer patients (see page 70).

Conclusion

Claims 44-47,50-52, 61, and 62 are objected because they depends on the rejected base claims. Claims 52, 56, 58-60, and 64-66 are allowed

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MISOOK YU whose telephone number is 571-272-0839. The examiner can normally be reached on 8 A.M. to 5:30 P.M., every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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SUPERVISORY PATENT EXAMINER
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